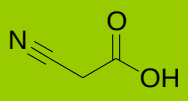
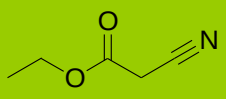
SIDS INITIAL ASSESSMENT PROFILE

Chemical Category Name	Cyanoacetates	
CATEGORY MEMBERS: **Chemical Names and CAS Registry Numbers**	Cyanoacetic acid 372-09-8	Ethyl cyanoacetate 105-56-6
Structural Formulas		

SUMMARY CONCLUSIONS OF THE SIAR

Category Justification

Ethyl cyanoacetate is the ethyl ester of cyanoacetic acid. Ethyl cyanoacetate hydrolizes rapidly under neutral and alkaline conditions to cyanoacetic acid and ethanol (and so it does under most physiological and environmental conditions), while in acid pH the half life is considerably longer. It also is likely that unspecific esterases in the body catalyze the hydrolysis to cyanoacetic acid and ethanol, as it has been shown for the structurally related ethyl acetate, which is rapidly hydrolyzed *in vitro and in vivo* by various esterases to yield ethanol and acetic acid. Ethanol is a physiological substance that is metabolized via physiological pathways. Ethanol (CAS. 64-17-5) was evaluated within the OECD HPV Chemicals Program. It can be assumed that for most endpoints cyanoacetic acid will be the common metabolite that determines the toxicity of both substances. Furthermore the production and use pattern of both, ester and acid, are comparable. As the acid and the ester have different physical chemical properties due to their chemical nature, effects that are related to the acidity of the acid (e.g. ecotoxicity data, local irritating effects) have to be assessed separately. The environmental and toxicokinetic distribution can however be expected to range in a similar order of magnitude due to the similar polarity, vapor pressure and log Kow. The biodegradation behavior is also expected to be comparable as the ester is probably cleaved and the metabolites further degraded.

Human Health

From the physical chemical properties of both cyanoacetic acid and ethyl cyanoacetate it can be expected that both substances will be moderately absorbed by all exposure routes. A relatively even distribution between tissues and also to embryonic tissues of pregnant rats was observed after oral administration of cyanoacetic acid. A similar behavior can be expected for ethyl cyanoacetate. Ethyl cyanoacetate is likely to be metabolized by unspecific esterases of different tissues, in particular in the liver to cyanoacetic acid and ethanol.

While no mortality and no signs of toxicity were observed in a 7-hour vapor inhalation study in rats with saturated vapors of cyanoacetic acid, the 4-hour LC_{50} in rats for an aerosol of 50 % cyanoacetic acid in water was 1900 mg/m^3. The most prominent symptoms were signs of severe irritation of eyes, mouth and respiratory tract. In a 1-hour inhalation study (according to US EPA DOT, 49 CFR, GLP) with ethyl cyanoacetate at the maximum attainable aerosol concentration of 7380 mg/m^3 the only substance related findings were reversible signs of irritation of the eyes and the upper respiratory tract. For cyanoacetic acid a dermal LD_{50} > 2000 mg/kg bw in rabbits was reported. In this study with limited documentation local irritant effects on the skin and some systemic effects (dyspnea, behavioral changes) were reported, indicating a possible systemic toxicity after dermal exposure. For ethyl cyanoacetate a dermal LD_{50} > 1000 and > 2000 mg/kg bw was reported in rabbits and rats, respectively, in studies in accordance with OECD TG 402 or 92/69/EEC B.3. No treatment related findings except for slight local skin irritation in the study in rabbits were observed. An acute oral LD_{50} value in rats of 1010 mg/kg bw has been reported for cyanoacetic acid. Symptoms including dyspnea, labored breathing, apathy and staggered gait were observed from doses of 1000 mg/kg bw and necropsy revealed local effects in the stomach. Only systemic effects similar to those reported for cyanoacetic acid were observed with ethyl

cyanoacetate at a limit dose of 2000 mg/kg bw in rats (studies in accordance with OECD TG 401 or EC 92/69/EEC B.1 and GLP).

Cyanoacetic acid was corrosive to rabbit skin (study according to Dir. 92/69/EEC, B.4. and GLP) and eyes (sufficiently documented study) while ethyl cyanoacetate was not irritating to rabbit skin (studies in accordance with OECD TG 404, GLP) and moderately irritating to rabbit eyes (study according to OECD TG 405, GLP). Based on the results of the inhalation toxicity studies, cyanoacetic acid can be regarded as highly irritating to the mucous membranes of the respiratory tract while ethyl cyanoacetate only had a slight irritant effect on the respiratory tract.

Both substances were not skin sensitizing in a Buehler test in guinea pigs according to US EPA OTS 798.4100 and GLP.

One 90-day oral (gavage) study in rats according to OECD TG 408 and GLP has been conducted with ethyl cyanoacetate at doses of 0, 100, 300 and 1000 mg/kg bw/day. The NOAEL in this study was 100 mg/kg bw/day for female rats and 300 mg/kg bw/day for male rats. A significant dose related reduction in hemoglobin values was observed at dose levels of 300 and 1000 mg/kg bw/day in female animals. In males of the 1000 mg/kg bw/day dose group increased urine volume and reversible pathological changes in liver (chronic peribiliary inflammation) and adrenals (vacuolization in the zona fasciculata of the adrenals) were observed. An additional examination of sperm counts and sperm motility in high dosed males revealed an apparently treatment related decrease in the percentage of motile sperms and sperm counts in the epididymis (changes within 2 standard deviations of the historical control data, no significant changes in organ weights or pathological findings in testes or epididymis). No effects were observed on female sex organs and estrous cycle.

Both cyanoacetic acid and ethyl cyanoacetate were not mutagenic in the standard Ames assay in bacteria with and without metabolic activation. Neither *Salmonella typhimurium* TA102 nor *E. coli* WP2 were tested in these Ames tests, however, this is an acceptable restriction, because it can be assumed that neither cyanoacetic acid nor ethyl cyanoacetate has oxidizing or cross-linking potential, which may be detected by TA102 or *E. coli* WP2. Ethyl cyanoacetate did not show any clastogenic activity in the *in vitro* cytogenetic assay with V79 Chinese Hamster lung cells in the presence and absence of a metabolic activation system. All tests with ethyl cyanoacetate were conducted according to OECD or EC guidelines and GLP. For both substances, there is no structural alert for genotoxicity. In conclusion, from the available information, there is no indication of a genotoxic potential of the substances, both for gene mutations and chromosomal aberrations.

No data are available on carcinogenicity.

No specific studies on fertility are available for cyanoacetic acid or ethyl cyanoacetate. In a 90-day oral gavage study (according to OECD TG 408 and GLP) with ethyl cyanoacetate that included a histopathological evaluation of the gonads as well as additional investigations on sperm motility and sperm counts a NOAEL for these fertility related endpoints of 300 mg/kg bw/day was derived. A decrease of sperm motility and epididymal sperm counts observed in this study at 1000 mg/m^3 (LOAEL) were not accompanied by significant reductions in testicular, epididymal, ovary or uterus weights, or any histopathological findings in these organs. Moreover, these effects are observed together with systemic toxicity.

In a developmental toxicity study with ethyl cyanoacetate according to OECD TG 414 and GLP the NOAEL for embryotoxic or fetotoxic effects was 100 mg/kg bw/day based on an increase in minor skeletal anomalies in litters of the 300 and 1000 mg/kg bw/day dose groups and a reduced mean fetal weight at 1000 mg/kg bw/day. The NOAEL for maternal toxicity in this study was 300 mg/kg bw/day. Maternal toxicity in this study was however, only defined based on clinical signs, body weight development and macroscopic organ changes. Therefore it can not be excluded that the observed developmental effects are due to maternal toxicity.

Studies on repeated dose toxicity and developmental toxicity conducted with ethyl cyanoacetate are considered relevant for cyanoacetic acid as well, as the ester will be rapidly metabolized to cyanoacetic acid and ethanol and its toxicity is likely to be mediated predominantly by cyanoacetic acid. Furthermore the study of the ester represents a “worst case” assumption for the acid as it can be assumed that the slightly more lipophilic ethyl ester is more readily absorbed than the corresponding acid and the maximum applicable dose of the ester is not limited by local irritation to mucous membranes. Therefore the ester can be administered at higher dose levels and is assumed to have a better bioavailability than the acid.

Environment

Cyanoacetic acid is a white crystalline solid; ethyl cyanoacetate is a colorless liquid. Cyanoacetic acid has a water

solubility of about 890 - 1000 g/l at 20 °C, a vapor pressure of 0.047 hPa at 25 °C and a measured log K_{OW} of -0.76. Ethyl cyanoacetate has a water solubility of 20 g/l at 25 °C, a vapor pressure of 0.05 hPa at 25 °C and a calculated log K_{OW} of 0.02. Ethyl cyanoacetate is readily biodegradable (95 to 100 % in a DOC-die away test, criteria of 10 day-window fulfilled) and undergoes hydrolytic degradation to cyanoacetic acid and ethanol. The half-life was ≤ 2.4 h (50 °C) at pH 9 and 7, and increased to 191 hours at pH 4 and 50 °C corresponding to 72 days at 25 °C. A photodegradation via oxidation by OH-radicals with half lives of about 25 days for cyanoacetic acid and 9 days for ethyl cyanoacetate in air was estimated. The generic fugacity model I indicates that both substances are preferably distributed in the water phase (> 99 % for both substances). The measured octanol-water partition coefficient (log K_{OW} -0.76 for cyanoacetic acid and 0.02 for ethyl cyanoacetate) and the calculated soil sorption coefficient (K_{OC} 1.0 for cyanoacetic acid and 4.1 for ethyl cyanoacetate) indicate a low potential for bio- or geoaccumulation.
Acute toxicity data for 3 trophic levels of the aquatic environment are available for ethyl cyanoacetate, and for 2 trophic levels for cyanoacetic acid. The 96 h LC_{50} for fish (*Leuciscus idus*) was 68 mg/l for cyanoacetic acid. This test was conducted without pH adjustment. A test with pH adjusted cyanoacetic acid solution with a satellite group of *Leuciscus idus* revealed only 10 % mortality after 96 h at a concentration of 215 mg/l. For ethyl cyanoacetate a 96 h LC_{50} of 59 mg/l was derived (*Danio rerio*). This test was conducted under flow-through conditions to ensure stability of the test concentration. The 48 h EC_{50} for *Daphnia magna* was 59 mg/l for cyanoacetic acid and 471 mg/l for ethyl cyanoacetate (nominal concentration). The 72 h E_rC_{50} for algae (*Scenedesmus subspicatus*) was 142 mg/l (72 h E_bC_{50} 72.4 mg/l) and the NOEC based on growth rate was 17 mg/l for ethyl cyanoacetate. It can reasonably be assumed that hydrolysis of the ester occurred in this study and the acid and the lowered pH have contributed considerably to the toxicity. Therefore the data of the ester are relevant for cyanoacetic acid as well. Acute toxicity tests for three trophic levels are available for ethyl cyanoacetate. According to the EU technical guidance document a $PNEC_{aqua}$ of 59 µg/l based on the lowest LC_{50} of 59 mg/l for fish can be derived for ethyl cyanoacetate using an assessment factor of 1000. Only two acute toxicity tests for fish and invertebrates are available for cyanoacetic acid. Therefore no $PNEC_{aqua}$ can be calculated. However, as ethyl cyanoacetate hydrolyzes quickly under environmental conditions the value for ethyl cyanoacetate may be relevant for cyanoacetic acid as well.

No growth inhibition of ethyl cyanoacetate to terrestrial plants in soil was observed up to concentrations of > 100 mg/kg soil (dry weight) and no toxicity to *Eisenia fetida* was observed at concentrations of 1000 mg ethyl cyanoacetate /kg soil (dry weight) after 14 days of exposure.

Exposure

In 2001 the estimated worldwide annual production capacity for cyanoacetates was more than 15 000 metric tons. The estimated annual production capacities were approximately 8000 metric tons in the US, 3500 metric tons in Europe, 3000 metric tons in Japan, 4000 metric tons in China and 1000 metric tons in India. Recent estimates of production capacities by the Sponsor Company for 2005 were 5000 metric tons in Europe, 12 000 metric tons in US, 800 metric tons in Japan, 1000 metric tons in India and 56 000 metric tons in China for cyanoacetic acid and for ethylcyanoacetate 6400 metric tons in US and 30 000 metric tons in China. The Sponsor Company imports ethyl cyanoacetate and cyanoacetic acid from its production site in USA to Germany where they are used as intermediates. Cyanoacetic acid and ethyl cyanoacetate are used as internal and external intermediates in the chemical industry; cyanoacetic acid for the production of photochemicals and flavor & fragrances ethyl cyanoacetate for the production of cyanoacrylate adhesives, pharmaceuticels, agrochemicals, dyes, photochemicals and UV-adsorbers. In the SPIN database there are no hints on other uses as the aforementioned.

From production at the Sponsor Company only limited exposure can be expected as both substances cyanoacetic acid and ethyl cyanoacetate are produced in a continuous closed system at Degussa AG. Waste water is sent at the sponsor's site to a biological waste water treatment plant, where it is completely degraded.

Short-term occupational exposure cannot be excluded during filling and sampling operations. Whenever a possible exposure is anticipated personal protective equipment consisting of goggles, face shield, gloves and chemical resistant suits is used. At the production site of Degussa AG and processing sites regular workplace measurements are not conducted

There are no data available on other production or processing sites in the Sponsor Country. There exist no occupational exposure limit values for cyanoacetic acid and ethyl cyanoacetate. No consumer products are listed to contain ethyl cyanoacetate in the Danish, Finnish, Norwegian and Swedish Product Registers. There are no data given on cyanoacetic acid in the Nordic Product Registers.

RECOMMENDATION AND RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

Human Health

The chemicals are candidates for further work. The chemicals possess properties indicating a hazard for human health (skin and eye corrosivity and respiratory irritation for cyanoacetic acid, at high doses effects on hematology, liver, adrenals and sperms after repeated dosing, embryotoxic or fetotoxic effects). Based on data presented by the Sponsor Company, exposure of workers during manufacturing in the Sponsor Company is anticipated to be low. The substances are not expected to be present in consumer products. As no worker exposure data is available on other production and processing sites in the Sponsor Country, it is recommended to conduct an exposure and if indicated a risk assessment at the workplace apart from the production site of the Sponsor Company.

Environment

The chemicals are currently of low priority for further work. The chemicals possess properties indicating a hazard for the environment (acute toxicity to fish [both substances] and invertebrates [cyanoacetic acid]). However, the chemicals are of low priority for further work because of their rapid biodegradation and limited potential for bioaccumulation. Countries may desire to investigate any exposure scenarios that were not presented by the Sponsor country